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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,623	08/27/2001	Xianxhang Yu	035879-0125	2349

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,623	YU ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-60 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-53 and 58-60 is/are rejected.

7)☐ Claim(s) 54-57 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/17/02+9/13/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S-d-C

DETAILED ACTION

1. Acknowledgement is made of applicants election of the species amoebapore and amoebapore homolog. After review of the claims in light of the prior art the species election is withdrawn.

2. Claims 1-60 are pending and examined on the merits.

Priority

3. Acknowledgement is made of Applicant's claim to an earlier effective filing date via 09/851,422, filed May 9, 2001; 60/203,063, filed May 9, 2000; and 60/212,042, filed June 16, 2000. Upon review of each of said applications, no support was found for a procytotoxin comprising a targeting molecule. Thus, the prior applications do not provide an adequate written description for the breath of the instant claims. Accordingly, the instant claims will be given the effective priority date of August 27, 2001.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12-14, 33-35 and 51-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims encompass a genus comprising analogs and derivative of all the species in claims 13, 34, and 52 as well as analogs and derivative of melittin. Every molecule recited in claims 13, 34, and 52 can be considered as a genus comprising analogs and derivatives of each. Each genus is highly variant because is tolerates species which differ substantially in

structure from the parent molecules. The specification provides not limitations which would allow one of skill in the art to determine if a given protein was indeed a member of the claimed genus, because the structural requirements for membership within the genus are not defined by the specification or set forth as a claim limitation. The specification does not provide examples of a representative number of species which fall within the bounds of each of the genuses. Thus, the disclosure of each of the parent molecules does not sufficiently describe the claimed genus, because the genus encompasses members which differ substantially in structure from the parent compounds. One of skill in the art would reasonably conclude that applicant was not in possession of the genuses encompassed by the claims It logically follows that method claims reliant upon the identify of a genus of products which are not adequately described, cannot itself be adequately described.

6. Claims 1-11, 21-32, 40-50, 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for how to make procytotoxins comprising cytolytic peptides having amphipathic alpha-helical structures and how to use said protoxins in the targeting of cancer cells, does not reasonably provide enablement for how to make procytotoxins which do not comprise amphipathic alpha-helical structures. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

When given the broadest reasonable interpretation, the "cytotoxin peptides" of the instant invention include any peptide based cytotoxin, such as gelonin, ricin, pseudomonas exotoxin, Dnase, Rnase, diphtheria toxin, pertussis toxin as well as the pore-forming cytolytic peptides which exhibit amphipathic alpha-helical structures. In the case of said pore-forming cytolytic peptides, there is a nexus between the cytolytic activity of the peptide and the specific three-dimensional structure of the peptide. It would be expected that attachment of peptides and amino acids via epsilon bonds to any of these peptides would inactivate said peptide because the ability to form the pore in a target cell is the result of the three dimensional structure and the property of the modified structure of one type of amphipathic alpha-helical structure would have a nexus with the modified structure of another type of amphipathic alpha-helical structure. However, the broadly based "cytotoxin peptides of the invention doe not have a similar structure so the result of structural modification cannot be predicted by analogy from amphipathic alpha-helical peptides. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make a procytotoxin comprising for instance, the cytotoxin of pseudomonas exotoxin because one of skill in the art would not know the structural requirements for the amino acid or peptide inactivator of the toxin, nor where to link the inactivator within the structure of the pseudomonas exotoxin molecule.

The specification states that another example of a cytolytic peptide can be found by screening cyclic D,L-alpha peptides for activity against mammalian cells and using said cyclic peptides isolated thereby to form structures wherein the peptide is attached to a peptide matrix metalloproteinase cleavage site which is linked via an epsilon bond to a microbead (paragraph 21). The specification cites Fernandez-Lopez et al (Nature, July 2001, Vol. 412, pp. 452-329) in support of the cyclic peptides. Upon review of said article it is noted that the peptides were optimized for adherence to adherence to bacterial cells. It is noted that one of the peptides (peptide 4) was screened for activity against a melanoma cell line. Fernandez-Lopez et al teach that the MIC against the melanoma cells is greater than 25 times the MIC for S aureus. Thus, in order to carry out the instant invention with cyclic peptides, one of skill in the art would be

required to optimize and screen for cyclic peptides that had lytic activity against mammalian cells. Such experimentation is in the realm of undue experimentation because it would precede the actual making of the modified structure.

Further, the art (Ghadiri, WO03092632) teaches that cyclic peptides are believed to self-assemble into supramolecular structures within or by association with cancer cell membranes, wherein said supramolecular structures (nanotubes, barrels of associated, axially parallel nanotubes, a carpet of associated nanotubes) can selectively induce cancer cell membrane depolarization or disruption while not depolarizing or disrupting normal cell membranes to a substantial or undesired degree. Thus, it can be reasonably concluded that it is the action of the supramolecular structure rather than the single molecule of cyclic peptide which exhibits cytotoxicity. Ghadiri (ibid) also teaches that small changes in amino acid sequence of a cyclic peptide can be amplified into large differences at the supramolecular level. Thus, changes in the structure of a cyclic peptide may constrain peptide interaction and limit formation of supramolecular structures to particular cellular membranes that have particular membrane constituents, membrane partitioning properties, uptake properties, and the like. It can be construed from this teaching that the modification of a cyclic peptide by means of attaching an amino acid or linker peptide via and epsilon bond, or attachment of a microbead, phage or phage filament, all of which are much larger than the single cyclic peptide molecule, would inhibit the formation of the supramolecular structure necessary for membrane selectivity. Further, an additional degree of complexity is added to the system because Ghadiri teaches that the assembly of the supramolecular structures occurs through association with the cancer cell membrane, because the cancer cell membrane in itself is complex and because different cancer cells would have different proteins on the membrane which could react in a different way with the modified cyclic peptide.

Given the lack of teachings in the specification regarding the issues above one of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed procytotoxins.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double-patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. In reBerg, 140 F.3d, 1428, 46 USPQ2d 1226 (Fed. Cir. 1998): In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993): In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

8. Claims 1, 2, 7, 12-15, 17, 18, 20-23, 28, 33-36 and 38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 09/851,422. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '422 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 1, 2, 4-10, 12-23, 25-31, 33-39 and 60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 09/851,422 in view of Glazier (U.S. 2003/0138432).

This is a provisional obviousness-type double patenting rejection.

Glazier teaches the targeting specific proteases of PSA (paragraphs 1329, 1354-1356), PSMA (paragraphs 710, 1015, 1019), matrix metalloproteinases (paragraphs 0698, 699 and 727-732). Glazier teaches the targeting of tumor neovasculature for drug delivery (paragraphs 958, 1291) and the use of the "RGD" targeting sequence (paragraphs 954-955). It would have been prima facie obvious at the time the invention was made to direct the procytotoxin of the invention to a tumor cell or the neovasculature surrounding a tumor cell to allow for more specificity of treatment. One of skill in the art would have been motivated to do so by the teachings of Glazier.

10. Claims 1, 2, 7, 12-15, 17, 18, 20-23, 28, 33-36 and 38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 11/131,443. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '443 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 54-57 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/11/2005

KAREN A. CANELLA PH.D
PRIMARY EXAMINER